EXPERT REVIEWS

Vaccines and febrile seizures

Expert Rev. Vaccines 12(8), 885–892 (2013)

Nicola Principi and Susanna Esposito*

Department of Pathophysiology and Transplantation, Pediatric Clinic 1, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy
**Author for correspondence:*
Tel.: +39 02 55032498
Fax: +39 02 50320206
susanna.esposito@unimi.it

Vaccine administration is the second leading cause of febrile seizures (FS). FS occurrence in children is a serious concern because it leads to public apprehension of vaccinations. This review discusses the clinical implications of FS, its potential link to vaccinations and its impact on official recommendations for vaccinations in children. Vaccines such as the pertussis antigen-containing vaccine, the measles-containing vaccine and the influenza vaccine have been linked to FS. However, FS events are very rare and are not usually associated with downstream complications or severe neurologic diseases. Considering their significant health benefits, vaccinations have not been restricted in the pediatric population. Nevertheless, vaccine-induced FS could be a problem, particularly in genetically predisposed children. Therefore, post-marketing surveillance studies are required to accurately assess the incidence of FS and identify individuals who are particularly susceptible to FS after vaccination.

KEYWORDS: febrile seizures • influenza vaccine • measles-containing vaccines • pertussis vaccines • prevention • vaccines • varicella vaccine

According to the American Academy of Pediatrics, febrile seizures (FS) occur in febrile children (6–60 months old) who do not have intracranial infection, metabolic disturbance or history of afebrile seizures [1]. FS affect 2–5% of children with a threefold higher risk in children between the ages of 6 and 16 months [1]. In addition to age, genetics [2,3], co-morbidities (e.g., premature birth and fetal growth retardation) [4,5] and environmental risk factors (*in utero* exposure to smoking or antihistamine use) [6,7] may further increase the risk of fever-induced seizures. FS have also been known to occur as a consequence of a sudden increase in body temperature to 39°C or higher. In the majority of cases, FS are defined as simple because they last for less than 15 minutes, are generalized without a focal component, and occur once in a 24-h period [1]. A small fraction of FS is complex because they are prolonged (>15 min), involve focal signs and recur during the same febrile episode [1]. Contrary to complex FS, which may be indicative of a pre-existing neurological problem, simple FS are benign even if they occur frequently. Children with simple FS exhibit normal neurologic and mental growth, and usually do not have increased risk of developing epilepsy [8]. Only those who have had several FS, are younger than 1 year at the time of their first FS and have a family history of epilepsy can have a negative prognosis with generalized afebrile seizures in 2.5% of the cases by 25 years of age [9].

Infections, particularly those involving the respiratory tract, are the most common cause of FS [10]. Vaccine administration is the second most common medical event associated with FS [1]. In children, fever is the most reported adverse effect following vaccination; however, the available data probably overestimates the impact of vaccines since many studies have included fevers that occurred in days after the vaccination had generated a biological response [11]. For instance, for a complication to be linked to vaccination, an event must occur no later than 72 h from inactivated vaccine administration and between 7 and 14 days from injection with live, attenuated vaccines [12]. Moreover, in almost all of the studies regarding safety and tolerability of vaccines, no comparison using a control group of unvaccinated children was included [12]. Consequently, the possibility remains that part of the observed febrile episodes considered to be caused by vaccine administration were due to other unidentified and confounding reasons. This idea was confirmed in a randomized, double-blind, placebo-controlled trial of measles, mumps and rubella (MMR) vaccines showing that 6% of children receiving placebo had developed fevers and that 88% of the fevers ≥38.5°C were unrelated to vaccination [13]. A possible explanation for this is that infections, extremely common in young children [14], may have contributed to higher fever rates in previous studies that did not control for infections occurring in the first days after vaccine administration.

10.1586/14760584.2013.814781

ISSN 1476-0584

Overall, most reported cases of fevers accompanying vaccine administration are generally well tolerated. Problems tend to arise when high fever is reported, thereby increasing the possibility of FS. Notably, this has been reported for the pertussis antigen– and measles-containing vaccines and, more recently, for influenza vaccines. Despite its low health risks, emergence of FS following vaccine administration could be considered a serious event by parents and some physicians and could result in negative attitudes toward vaccinating children. A questionnaire study found that witnessing an FS was a frightening experience for parents and that parental fear of FS was a major problem with several negative consequences for daily family life [15]. Moreover, physicians themselves have problems in this regard and generally prefer to administer vaccines with a lower risk of FS than products with a supposed increased risk [16]. Here, we discuss the association of FS with vaccine administration and how this relationship has impacted vaccination regimens in children.

Pertussis antigen-containing vaccines

For many years the whole cell pertussis (wcP) vaccine had been the only vaccine available for pertussis infection. Immediately after its introduction to the market, it was found that its administration seemed to correlate with local and systemic reactions in a subset of children. These complications included a very severe clinical picture with high fever, FS and epileptic encephalopathy (referred to as Dravet syndrome) [17]. These negative and neurologic events were highly publicized, which led to the reduction of pertussis vaccinations in many countries and, consequently, pertussis epidemics [18]. Later it was shown that Dravet syndrome is not directly associated with wcP vaccination and depends on a genetic defect involving a mutation in the SCN1A sodium channel gene. Fever, due to vaccination, may have been a factor simply triggered by the onset of disease [19]. This conclusion is further supported by evidence that the late onset of Dravet syndrome in children did not differ significantly between vaccinated and unvaccinated FS patients [20]. However, an association between wcP vaccination and an increased risk of developing FS was considered a valid and well-documented phenomenon. Reports concerning the administration of wcP vaccine in combination with diphtheria and tetanus vaccines and the occurrence of FS have been documented [21–23]. A complete evaluation of all studies regarding the use of wcP-containing vaccines showed that the overall risk of FS was relatively uncommon [21]. However, these reports were limited to the period immediately following vaccination and follow-up reports of neurological complications were not documented. A meta-analysis on earlier studies regarding DTwcP vaccines found that the relative risk (RR) of FS was 1.8 (95% CI: 1.2–2.7) [21]. Higher RR of FS up to 3 days after DTwcP injection was later reported by Farrington *et al.* (RR: 3.0; 95% CI: 1.6–5.5), although this was correlated with only the third dose of the vaccine [22]. Finally, in a study by Barlow *et al.*, it was shown that receiving the DTwcP vaccine was associated with an increased risk of FS only on the day of vaccination (RR: 5.70; 95% CI: 1.98–16.42) without any significant risk of subsequent seizures or neurodevelopment disabilities [23]. The number of FS attributable to the use of this vaccine was estimated to vary from 6 to 9 per 100,000 children. Collectively, these findings explain why health authorities, lacking safer pertussis vaccines continued to recommend wcP-containing vaccines. On the other hand, the severity of pertussis in infants and the efficacy of wcP-containing vaccines largely justified the mild risks associated with vaccine administration [24].

More recently, the less reactogenic acellular pertussis vaccine (aP) has been introduced and has become widely available in most of the industrialized countries. However, the DTwcP vaccine is still in use in many developing countries because it is significantly cheaper [25]. Several studies involving DTaP were performed to test its safety and tolerability, including the occurrence of FS. In the first set of studies there was no significant difference in FS incidence between patients receiving aP vaccines and those who received wcP [26–29]. However, these studies had limits because they were not powered to assess rare adverse events. Moreover, two of the three studies indicated that certain preparations of the aP vaccine may confer increased risk of FS. They found that on the day of vaccination, children receiving diphtheria–tetanus toxoids–aP-inactivated polio–*Haemophilus influenzae* type b (DTaP-IPV-Hib) [30] or DTaP vaccine [31] had a twofold and 30% higher risk of seizures, respectively, although these estimates did not reach statistical significance. Moreover, the studies did not distinguish between afebrile seizures and FS. Only one study clearly showed a potential negative effect of aP [32]. In this cohort study, 378,834 children were followed up for several years and it was found that incidence of FS was more frequent after vaccine administration than in other periods of time. In particular, it was reported that despite the pertussis component of the vaccine used (DTaP-IPV-Hib vaccine) being made by only one antigen instead of three antigens as in other studies, RR of FS was increased on the day of the first and the second vaccinations even if not on the day of the third vaccine administration. However, it was calculated that the absolute risk was low (<four per 100,000 vaccinations). Moreover, the overall risk of FS was not increased within 0–7 days after vaccinations, as it was the risk of recurrent FS or subsequent epilepsy. In conclusion, aP-containing vaccines have a marginal role, if any, in causing FS. This is in agreement with the very low local and systemic reactogenicity reported for these preparations [33].

Measles-containing vaccines

The relationship between the MMR vaccine administration and the development of FS has been extensively studied [22,34,35]. It has been documented that seizures can occur in children 1–2 years of age during the second week following the first vaccination. FS are ascribed to the measles component of the trivalent vaccine. Barlow *et al.* examined medical records of 137,457 MMR vaccine recipients and reported that its administration was associated with seizures at an RR of 2.83 (95% CI: 1.44–5.55) from 8 to 14 days after vaccination. No elevated risk was found in the first week or 15–30 days following vaccination [23]. The same authors used background rates of seizures derived from different data sources and found that MMR vaccine administration increased the number of FS cases by 25.0 to 34.2 per 100,000 children [23].

The second dose of the MMR vaccine to 4- to 6-year-old children has not been linked to febrile neurologic problems [36]. Follow-up cohort studies have shown that children experiencing their first FS after MMR vaccination were equally prone to recurrent seizures than unvaccinated children who suffered from FS [23,34]. Moreover, none of the patients experienced nonfebrile seizures or were diagnosed with epilepsy. In addition, risk of FS was greater in those who had previously experienced episodes of FS and in those with a family history of seizures, regardless of vaccination [37]. On the basis of these findings, it was concluded that the potential risk of developing FS after the first MMR vaccination was not sufficient to dismiss the use of MMR vaccine. Therefore, this vaccine has been widely recommended to children. However, as a precaution, American health authorities have recommended that parents of children receiving MMR vaccine should remain vigilant and informed of appropriate actions if fever ensues [38].

With the approval of the tetravalent measles, mumps, rubella and varicella (MMRV) vaccine in the USA (2005), new problems regarding FS and vaccinations occurred. The pre-licensed studies of the vaccine, ProQuad®, showed an increased occurrence of fever at 5–12 days and 0–42 days after the first dose compared to the MMR vaccine and varicella (V) vaccine [39]. Moreover, post-licensure observational studies not only confirmed the increased occurrence of fever, but also showed that FS were significantly more common. Jacobsen *et al*. reported that among 31,298 children between the ages of 12–60 months who received either MMRV or MMR+V vaccination for the first time, 22 (0.70/1,000) and ten (0.32/1,000) cases (RR: 2.20; 95% CI: 1.04–4.65), respectively, suffered from febrile seizures 5–12 days following vaccination [40]. Klein *et al*. with a cohort study assessed seizures and fever visits among children aged 12–23 months after MMRV and separate MMR+V vaccines and found that among the 83,107 MMRV vaccine recipients seizure risk during days 7–10 after vaccination was higher than among 376,354 children given MMR+V (RR: 1.98 [95% CI: 1.43–2.73]) with an excess risk of 0.43 per 1000 doses (95% CI: 2.6–5.6) [41].

Despite these previous findings, American health authorities initially (2008) concluded that the use of vaccines containing multiple antigens could maximize vaccination coverage and showed no preference between MMRV or MMR+V vaccines [42]. However, their stance changed when a more complete analysis of epidemiological data was performed confirming that the first dose of MMRV vaccine was more reactogenic than that of MMR+V vaccines, whereas a second dose of the tetravalent vaccine was not associated to increased health risks in children [43]. Starting from these data, the Advisory Committee on Immunization Practice of the USA stated that for the first vaccination MMRV vaccine or MMR+V vaccines might be administered to 1–2 year olds, and that, after discussion between the provider and parents, families without a strong preference for MMRV vaccine should receive MMR+V vaccines [44]. On the contrary, MMRV could be used for the second dose. Similar conclusions were reached in Germany with a different formulation of MMRV (Priorix-Tetra®) [101]. This stemmed from meta-analyses reports on clinical studies of Priorix-Tetra®, which showed that combined vaccine was more reactogenic than MMR+V vaccines and fever was more frequently associated with seizures. Although the incidence of FS in this case was not statistically significant, this result was considered sufficient to warn about the use of MMRV. The Standing Committee on Vaccination at the Robert Koch Institute in Germany, following consultations with the EMA decided to revise the technical information on Priorix-Tetra® and include a sentence declaring that the MMR and V vaccines have to be preferred for the first tetravalent vaccination and MMRV vaccine could be used for the second dose [101].

Vaccination against MMRV is widely available for children, and while health authorities show a preference for separate MMR and V vaccinations, the option to use MMRV vaccine is still available for parents and physicians. This could potentially limit vaccine coverage in children for MMR and/or V vaccines. A recent survey, carried out in a period of time during which MMRV vaccine was on the market, assessing knowledge, beliefs, attitudes, and intended practices regarding the MMRV vaccine and its relationship to FS found that, after reading an informational statement, only 20% of pediatricians and 7% of family physicians would recommend the MMRV vaccine to a healthy 12–15-month-old child [16]. These findings indicate that, in most cases, separate injections of MMR and V vaccines were chosen despite requiring more deferrals or injections.

Influenza vaccines

Since its approval for use in children, the trivalent inactivated influenza vaccine (TIV) has been considered safe and well tolerated without any known risk of acute neurological events. In the years after its release, no increases in the occurrence of seizures were reported the week following vaccination [45–48]. Moreover, no increase in the incidence of influenza vaccine-related FS was reported in the 2009–2010 influenza season, despite the increased number of vaccinations in young children with a monovalent vaccine designed to prevent pandemic influenza [49,50]. Despite these reassuring outcomes, a safety alert for FS associated with influenza vaccination was issued in April 2010. In Australia, it was reported that an increase in the number of children less than 5 years of age (median age 1.5 years) had suffered from fever and FS after having received the 2010 Southern Hemisphere TIV formulation (Fluvax® and Fluvax® junior) [51]. In the majority of cases, seizures occurred within 12 h of vaccination at a rate of 3.3 cases per 1000 TIV doses. This rapid onset of fever and seizures, together with immediate recovery, supported the hypothesis that seizures were induced by high fevers in predisposed children as opposed to being provoked by vaccine-related neurological or metabolic toxicities [52]. This resulted in a temporary suspension of all influenza vaccinations in Australian children [53]. Furthermore, it was recommended that Fluvax and Fluvax junior vaccines not be used in children aged 6 months to 8 years in the USA [54]. An observational study carried out in New Zealand investigated four TIVs manufactured by different companies for children between the ages of 6 months and 5 years. It was confirmed that Fluvax had higher reactogenicity and despite having similar antigenic compositions, the other TIVs had significantly

lower risk of febrile reactions and seizures [55]. Additionally, it was reported that FS occurred only after Fluvax administration in addition to higher frequency of fevers. However, Influvac® had higher rates of febrile reactions (OR: 0.54; 95% CI: 0.36–0.81) than Vaxigrip® (OR: 0.21; 95% CI: 0.16–0.27) and Fluarix® (OR: 0.10; 95% CI: 0.05–0.20).

Because β-propiolactone was used to make Fluvax instead of formaldehyde as in the other influenza vaccines, it was believed that this manufacturing process led to incomplete disruption of virion particles and enhanced pyrogenicity of Fluvax [56,57]. On the other hand, with an *in vitro* model, Blyth *et al*. were able to demonstrate that Fluvax injections, in comparison to other TIVs, led to higher induction of IFN-α, IL-6 and IL-1β [52,58]. This response resembled the effect of treatment with inactivated influenza A virus *in vitro* [59] or infection with natural influenza [59,60]. However, what happened in the USA during the 2010–2011 influenza season supports the hypothesis that the problem of vaccination-associated FS could not be ascribed only to Fluvax [61,62]. During that influenza season, the Centers for Disease Control and Prevention and the US FDA conducted enhanced vaccine safety monitoring for possible febrile seizures in all TIV products in the USA using the vaccine adverse event reporting system (VAERS) [61]. Empirical Bayesian data mining techniques were used to assess disproportionate reporting after TIV and febrile seizure reports in children aged <5 years were reported. On 23 November 2010 the combination of the coding term 'febrile convulsion' and the Fluzone® TIV product exceeded a predetermined threshold in the VAERS database. By 10 December, 43 reports of febrile seizure following TIV in children aged 6–23 months were confirmed. Moreover, a study with a cohort of 206,174 children aged 6–59 months demonstrated that Fluzone vaccinations significantly increased the risk of FS [62]. The highest risk was demonstrated in children who had received TIV together with 13-valent pneumococcal conjugate vaccine (PCV13), although single influenza and pneumococcal vaccinations were also associated with increased risk of FS. The incidence rate ratio (IRR) for TIV adjusted for concomitant PCV13 was 2.4 (95% CI: 1.2–4.7), PCV13 adjusted for concomitant TIV was 2.5 (95% CI: 1.3–4.7) and concomitant TIV and PCV13 was 5.9 (95% CI: 3.1–11.3), suggesting that the concomitant administration of both vaccines could be significantly more dangerous. Moreover, RR varied as a function of age with the highest estimates occurring at 16 and the lowest at 59 months (45 and four per 100,000 doses for TIV with concomitant PCV13, respectively) with a trend quite similar to that demonstrated for febrile seizures associated with infectious diseases [62].

A number of hypotheses have been advanced to explain the recent emergence of vaccine-induced FS after influenza vaccine administration. It was supposed that the risk of FS in children had not been initially discovered due to its low incidence in children [62]. Moreover, it was thought that differences in incidence of TIV-related FS between older and more recent epidemiological studies could simply be due to the changes in the definition of risk interval [62]. In older studies, occurrence of FS was monitored for up to 1 week, whereas in recent studies only events in the first 24 h are recorded. A re-calculation of older data using the first day risk interval did not reveal increased risk of FS, suggesting that TIV injection was not an underlying cause. Another explanation, which was likely wrong, was that the presence of pandemic virus in the TIV used for the 2010–2011 season could have modified the reactogenicity of the vaccine although the methods used for the preparation of the vaccine were exactly the same as for previous influenza vaccines [62], which were not associated with increased risk of FS [63–65]. Finally, it was suggested that the host-specific factors may play a role in the development of seizures. In New Zealand, it was found that patients of European decent were more likely to develop a fever within 24 h of vaccination [55]. Ethnic origin has been implicated in variable immunogenicity to hepatitis B [65] and reactogenicity to the anthrax vaccine [66]. However, genetic characteristics can underlie the immune response and reactogenicity to TIV, but they do not explain the emergence of influenza vaccine–related seizures in a population that had previously been exposed to the same vaccine.

Despite not being solved, the problem of the increased risk of febrile seizures after TIV administration in younger children has led to several practical consequences. In the USA, vaccination against influenza with approved TIV was not discouraged, although the risk of FS was obvious. However, particular attention was paid not only to TIV but also to the simultaneous administration of TIV and PCV13, since co-injection conferred higher risk of FS [67]. However, since both vaccines were considered to be essential for children by the American health authorities, co-injection was still recommended. ACIP highlighted the need for education of providers and parents on the risks and benefits of vaccines [67]. Moreover, the labels for Fluzone and for PCV13 warned users of the associated risk of FS [67]. In Europe, when it was shown that virosomal-adjuvanted influenza vaccine, approved for use in younger children, could cause a fever of ≥38°C in approximately 15% of recipients and >39°C in approximately 5% of the cases, although not accompanied by FS [68], warnings in the package insert were included [102].

Because the origin of TIV-related FS and whether its effects are brand-specific is not known, further studies on the immediate effects of TIV administration are mandatory. These have to include the live attenuated influenza vaccine, despite the fact that this vaccine has a very low risk of fever and adverse neurologic events [69].

Expert commentary

For some vaccines, such as pertussis antigen-containing vaccines, measles-containing vaccines and influenza vaccines, there exists an association between vaccination and increased risk of FS. However, the risk of severe consequences is very low since associated FS are not usually followed by any further neurologic disorders. Considering the efficacy of these vaccines in reducing the risk of disease with significant clinical, social and economic impact, the benefits of vaccination outweigh its risks. This explains why health authorities have not restricted the use of these vaccines in the pediatric population although they have clearly indicated that when different preparations of the same vaccine are

available, it is recommendable to administer the preparation or to use the schemes of administration with the lowest documented risk of FS. Acellular pertussis vaccine has to be preferred to the whole cell pertussis vaccine, whereas at least for the first administration, MMR and V vaccine have to be administered separately. Despite less common than the episodes associated with measles containing vaccines or wcP vaccines, further studies are needed to understand the mechanism of influenza vaccine–induced FS and whether co-administration with other vaccines increases the risk of FS. The yearly use of influenza vaccines universally recommended in children today justifies particular attention to this kind of prevention.

Five-year view

Although vaccine-induced FS is a rare phenomenon that does not lead to deleterious outcomes, it could impact patient and physician attitude toward the safety of vaccination. For this reason, the incidence and timing of vaccine-induced fever and FS has to be precisely quantified. Moreover, genetic factors associated with risk need to be identified. In this way, children most susceptible to vaccine-induced FS can be treated with antipyretics, which reduce fever, prior to vaccination [70,71]. Indeed, ibuprofen and acetaminophen can reduce the possibility of fever following DTaP immunization in children with a history of febrile seizures [72]. Vaccine-induced FS is a rare phenomenon that occurs mainly in genetically predisposed children. Moreover, as reported for the simultaneous administration of influenza and pneumococcal vaccines, the associated risks could be enhanced when vaccines are administered in combination. Moreover, even if recently performed studies on vaccine safety and tolerability have included tens of thousands of participants, adverse but rare events such as FS can be missed. Finally, because most immunizations are administered in the first months of life, an accurate estimation of FS-prone children is not possible since detailed clinical history is frequently missed in infants. Only an extensive and thorough post-marketing study can accurately address these problems. This is particularly important for those vaccines that have caused fever in pre-marketing studies and that are frequently administered with other vaccines. The recent multicomponent, recombinant meningococcal serogroup B (4CMenB) vaccine is an example. A recent study has showed that increased reactogenicity is associated with this vaccine when it is administered concomitantly with routine vaccines (DTaP-IPV-HBV-Hib and PCV7) [73]. Seventy seven percent (1912 out of 2478) of infants had a fever of 38.5°C or higher after 4CMenB injection, compared to only 45% (295 out of 659) after routine vaccinations alone and 47% (228 out of 490) with *Neisseria meningitidis* group C co-vaccination [73]. Although only two FS events were associated with 4CMenB injections, this problem deserves particular attention and requires further studies.

Financial & competing interests disclosure

This review was supported by a grant from the Italian Ministry of Health (Ricerca Corrente Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico 850/01 2012). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Notwithstanding the obvious health benefits of vaccination, occurrence of febrile seizures (FS) following injections could be considered by parents and some physicians as a relevant clinical problem.
- FS events could act as a deterrent for public support of vaccinations.
- Administration of some vaccines such as pertussis antigen-containing vaccines, measles-containing vaccines and influenza vaccines confer a low risk of FS.
- For those vaccines for which different preparations exist (e.g., in the case of pertussis and measles-containing vaccines), it is reasonable to use those preparations (acellular instead of whole cell pertussis vaccine) or those schemes of administration (measles, mumps and rubella + varicella instead of measles, mumps, rubella and varicella) that carry a significantly lower risk of FS.
- In the case of influenza vaccines, further studies are needed to evaluate various brands and whether co-administrations with other vaccines significantly increase the risk of FS.
- Considering that FS events are rare, only post-marketing surveillance can accurately assess the risk of vaccination.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 121, 1281–1286 (2008).

2 Kjeldsen MJ, Kyvik KO, Friis ML, Christensen K. Genetic and environmental factors in febrile seizures: a Danish population-based twin study. *Epilepsy Res.* 51(1–2), 167–177 (2002).

3 Offringa M, Bossuyt PM, Lubsen J *et al.* Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J. Pediatr.* 124(4), 574–584 (1994).

4 Herrgård EA, Karvonen M, Luoma L *et al.* Increased number of febrile seizures in children born very preterm: relation of neonatal, febrile and epileptic seizures and neurological dysfunction to seizure outcome at 16 years of age. *Seizure* 15(8), 590–597 (2006).

5 Visser AM, Jaddoe VW, Hofman A *et al.* Fetal growth retardation and risk of febrile seizures. *Pediatrics* 126(4), e919–e925 (2010).

6 Vestergaard M, Christensen J. Register-based studies on febrile seizures in Denmark. *Brain Dev.* 31(5), 372–377 (2009).

7 Takano T, Sakaue Y, Sokoda T *et al.* Seizure susceptibility due to antihistamines in febrile seizures. *Pediatr. Neurol.* 42(4), 277–279 (2010).

8 Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. *N. Engl. J. Med.* 295(19), 1029–1033 (1976).

9 Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. *N. Engl. J. Med.* 316(9), 493–498 (1987).

10 Millichap JG, Millichap JJ. Role of viral infections in the etiology of febrile seizures. *Pediatr. Neurol.* 35(3), 165–172 (2006).

11 Kohl KS, Marcy SM, Blum M *et al.*; Brighton Collaboration Fever Working Group. Fever after immunization: current concepts and improved future scientific understanding. *Clin. Infect. Dis.* 39(3), 389–394 (2004).

12 Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage'. *Curr. Opin. Neurol.* 20(2), 181–187 (2007).

13 Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. *Lancet* 1(8487), 939–942 (1986).

14 Griffin MR, Walker FJ, Iwane MK, Weinberg GA, Staat MA, Erdman DD; New Vaccine Surveillance Network Study Group. Epidemiology of respiratory infections in young children: insights from the new vaccine surveillance network. *Pediatr. Infect. Dis. J.* 23(11 Suppl), S188–S192 (2004).

15 van Stuijvenberg M, de Vos S, Tjiang GC, Steyerberg EW, Derksen-Lubsen G, Moll HA. Parents' fear regarding fever and febrile seizures. *Acta Paediatr.* 88(6), 618–622 (1999).

16 O'Leary ST, Suh CA, Marin M; Vaccine Policy Collaborative Initiative. Febrile seizures and measles-mumps-rubella-varicella (MMRV) vaccine: what do primary care physicians think? *Vaccine* 30(48), 6731–6733 (2012).

- **After this study evaluating data regarding febrile seizure risk after measles, mumps, rubella and varicella (MMRV), few physicians report they would recommend MMRV to a healthy 12 to 15-month-old child.**

17 Tro-Baumann B, von Spiczak S, Lotte J *et al.* A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome. *Epilepsia* 52(1), 175–178 (2011).

18 Baker JP. The pertussis vaccine controversy in Great Britain, 1974–1986. *Vaccine* 2, 14003–14010 (2003).

19 Berkovic SF, Harkin L, McMahon JM *et al.* De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol.* 5(6), 488–492 (2006).

20 McIntosh AM, McMahon J, Dibbens LM *et al.* Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol.* 9(6), 592–598 (2010).

21 Institute of Medicine, Committee to review the adverse consequences of pertussis and rubella vaccines. Adverse Effects Of Pertussis And Rubella Vaccines. National Academy Press, Washington, DC, USA (1991).

22 Farrington P, Pugh S, Colville A *et al.* A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 345(8949), 567–569 (1995).

23 Barlow WE, Davis RL, Glasser JW *et al.*; Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N. Engl. J. Med.* 345(9), 656–661 (2001).

24 Hampl SD, Olson LC. Pertussis in the young infant. *Semin. Respir. Infect.* 10(1), 58–62 (1995).

25 Singh M, Lingappan K. Whooping cough: the current scene. *Chest* 130(5), 1547–1553 (2006).

26 Greco D, Salmaso S, Mastrantonio P *et al.* A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. *N. Engl. J. Med.* 334(6), 341–348 (1996).

27 Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N. Engl. J. Med.* 334(6), 349–355 (1996).

28 Trollfors B, Taranger J, Lagergård T *et al.* A placebo-controlled trial of a pertussis-toxoid vaccine. *N. Engl. J. Med.* 333(16), 1045–1050 (1995).

29 Decker MD, Edwards KM, Steinhoff MC *et al.* Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics* 96(3 Pt 2), 557–566 (1995).

30 Andrews N, Stowe J, Wise L, Miller E. Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom. *Vaccine* 28(44), 7215–7220 (2010).

31 Huang WT, Gargiullo PM, Broder KR *et al.*; Vaccine Safety Datalink Team. Lack of association between acellular pertussis vaccine and seizures in early childhood. *Pediatrics* 126(2), 263–269 (2010).

32 Sun Y, Christensen J, Hviid A *et al.* Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. *JAMA* 307(8), 823–831 (2012).

- **A well-conducted study showing that diphtheria–tetanus toxoids–aP-inactivated polio–*Haemophilus influenzae* type b vaccination was associated with an increased risk of febrile seizures but not of epilepsy on the day of the first two vaccinations given at 3 and 5 months, although the absolute risk was small.**

33 Rosenthal S, Chen R, Hadler S. The safety of acellular pertussis vaccine vs whole-cell pertussis vaccine. A postmarketing assessment. *Arch. Pediatr. Adolesc. Med.* 150(5), 457–460 (1996).

34 Griffin MR, Ray WA, Mortimer EA, Fenichel GM, Schaffner W. Risk of seizures after measles-mumps-rubella immunization. *Pediatrics* 88(5), 881–885 (1991).

35 Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *Am. J. Epidemiol.* 165(6), 704–709 (2007).

36 Davis RL, Marcuse E, Black S *et al.* MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink project. The Vaccine Safety Datalink Team. *Pediatrics* 100(5), 767–771 (1997).

37 Centers for Disease Control and Prevention. Adverse Events Following Immunization. US Department of Health and

Human Services, Public Health Service, CDC, Atlanta, GA, USA. Surveillance Report no. 3, 1985–1986 (1989).

38 Centers for Disease Control and Prevention. Measles, mumps, and rubella – vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb. Mortal. Wkly. Rep.* 47(No. RR-8), 38–39 (1998).

39 Centers for Disease Control and Prevention. Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. *MMWR Morb. Mortal. Wkly. Rep.* 57, 258–260 (2008).

40 Jacobsen SJ, Ackerson BK, Sy LS *et al.* Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* 27(34), 4656–4661 (2009).

41 Klein NP, Fireman B, Yih WK *et al.*; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics* 126(1), e1–e8 (2010).

42 Centers for Disease Control and Prevention. Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. *MMWR Morb. Mortal. Wkly. Rep.* 57, 258–260 (2008).

43 Klein NP, Lewis E, Baxter R *et al.* Measles-containing vaccines and febrile seizures in children age 4 to 6 years. *Pediatrics* 129(5), 809–814 (2012).

•• **This study provides reassurance that MMRV and MMR+V were not associated with increased risk of febrile seizures among 4- to 6-year-olds.**

44 Marin M, Broder KR, Temte JL, Snider DE, Seward JF; Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Recomm. Rep.* 59(RR-3), 1–12 (2010).

45 Hambidge SJ, Glanz JM, France EK *et al.*; Vaccine Safety Datalink Team. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA* 296(16), 1990–1997 (2006).

46 Greene SK, Kulldorff M, Lewis EM *et al.* Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am. J. Epidemiol.* 171(2), 177–188 (2010).

47 Glanz JM, Newcomer SR, Hambidge SJ *et al.* The safety of trivalent inactivated influenza vaccine in children ages 24 to 59 months. *Arch. Pediatr. Adolesc. Med.* 165, 749–755 (2011).

48 Lee GM, Greene SK, Weintraub ES *et al.*; Vaccine Safety Datalink Project. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *Am. J. Prev. Med.* 41(2), 121–128 (2011).

• **A well-performed surveillance showing that no major safety problems following H1N1 or seasonal influenza vaccines were detected in the 2009–2010 season in weekly sequential analyses.**

49 Salmon DA, Akhtar A, Mergler MJ *et al.*; H1N1 Working Group of Federal Immunization Safety Task Force. Immunization-safety monitoring systems for the 2009 H1N1 monovalent influenza vaccination program. *Pediatrics* 127 Suppl 1, S78–S86 (2011).

• **The effort to vaccinate the USA population against the 2009 H1N1 influenza virus improved monitoring of 2009 H1N1 vaccine safety, holding promise for enhancing future national monitoring of vaccine safety, and helping improve public confidence in vaccines.**

50 Stowe J, Andrews N, Bryan P, Seabroke S, Miller E. Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study. *Vaccine* 29(51), 9467–9472 (2011).

51 Armstrong PK, Dowse GK, Effler PV *et al.* Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent inactivated influenza vaccine. *BMJ Open* 1(1), e000016 (2011).

52 Blyth CC, Currie AJ, Wiertsema SP *et al.* Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. *Vaccine* 29(32), 5107–5113 (2011).

• **Numerous febrile adverse events (including febrile seizures) were observed following Fluvax® or Fluvax® junior in 2010. Clear differences in cytokine production were observed when peripheral blood mononuclear cells were stimulated with Fluvax compared with alternate TIV preparations. Increased awareness of these potential adverse events is required to ensure earlier detection and prevention in the future.**

53 Department of Health and Aging, editor. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Australian Government Therapeutic Goods Administration (2010).

54 Centers for Disease Control and Prevention. Update: recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States During 2010–11. *MMWR Morb. Mortal. Wkly Rep.* 59, 989–992 (2010).

55 Petousis-Harris H, Poole T, Turner N, Reynolds G. Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: the importance of routine active safety surveillance. *Vaccine* 30(33), 4945–4952 (2012).

• **A study showing that influenza vaccines have different rates of reactogenicity in children, which varies between ethnic groups. High rates of febrile convulsions and reactions in children receiving Fluvax and to a lesser extent the higher fever rates in those receiving Influvac® compared with the other two brands of influenza vaccines in this study suggest that reactogenicity profiles need to be considered prior to national policy advice each season.**

56 Kelly HA, Skowronski DM, De Serres G, Effler PV. Adverse events associated with 2010 CSL and other inactivated influenza vaccines. *Med. J. Aust.* 195(6), 318–320 (2011).

57 Maraskovsky E, Rockman S, Dyson A *et al.* Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine. *Vaccine* 30(51), 7400–7406 (2012).

58 Bussfeld D, Kaufmann A, Meyer RG, Gemsa D, Sprenger H. Differential mononuclear leukocyte attracting chemokine production after stimulation with active and inactivated influenza A virus. *Cell. Immunol.* 186(1), 1–7 (1998).

59 Hayden FG, Fritz R, Lobo MC, Alvord W, Strober W, Straus SE. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. *J. Clin. Invest.* 101(3), 643–649 (1998).

60 Masuyama T, Matsuo M, Ichimaru T, Ishii K, Tsuchiya K, Hamasaki Y. Possible contribution of interferon-alpha to febrile seizures in influenza. *Pediatr. Neurol.* 27(4), 289–292 (2002).

61 Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010–2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. *Vaccine* 30(11), 2020–2023 (2012).

62 Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine* 30(11), 2024–2031 (2012).

•• **Demonstrates that incidence rate ratio and risk difference estimates were lower for children receiving TIV without concomitant PCV13 or PCV13 without concomitant TIV. Because of the importance of preventing influenza and pneumococcal infections and associated complications, the authors concluded that their findings should be placed in a benefit-risk framework to ensure that population health benefits are maximized.**

63 Esposito S, Pugni L, Daleno C *et al.* Influenza A/H1N1 MF59-adjuvanted vaccine in preterm and term children aged 6 to 23 months. *Pediatrics* 127(5), e1161–e1168 (2011).

64 Nolan T, Bernstein DI, Block SL *et al.*; LAIV Study Group. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Pediatrics* 121(3), 508–516 (2008).

65 Poland GA, Ovsyannikova IG, Jacobson RM. Application of pharmacogenomics to vaccines. *Pharmacogenomics* 10(5), 837–852 (2009).

66 Pittman PR, Gibbs PH, Cannon TL, Friedlander AM. Anthrax vaccine: short-term safety experience in humans. *Vaccine* 20(5-6), 972–978 (2001).

67 Broder KR, Martin DB, Vellozzi C. In the heat of a signal: responding to a vaccine safety signal for febrile seizures after 2010-11 influenza vaccine in young children, United States. *Vaccine* 30(11), 2032–2034 (2012).

• **An overview on the demonstrated increased risk of FS after administration of some trivalent inactivated influenza vaccine preparations.**

68 Esposito S, Marchisio P, Montinaro V *et al.* The immunogenicity and safety of a single 0.5 mL dose of virosomal subunit influenza vaccine administered to unprimed children aged =6 to <36 months: data from a randomized, Phase III study. *Vaccine* 30(49), 7005–7012 (2012).

69 Mallory RM, Malkin E, Ambrose CS *et al.* Safety and immunogenicity following administration of a live, attenuated monovalent 2009 H1N1 influenza vaccine to children and adults in two randomized controlled trials. *PLoS ONE* 5(10), e13755 (2010).

70 Lewis K, Cherry JD, Sachs MH *et al.* The effect of prophylactic acetaminophen administration on reactions to DTP vaccination. *Am. J. Dis. Child.* 142(1), 62–65 (1988).

71 Ipp MM, Gold R, Greenberg S *et al.* Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids-polio vaccine. *Pediatr. Infect. Dis. J.* 6(8), 721–725 (1987).

72 Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children – recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb. Mortal. Wkly Rep.* 46(RR-7), 19 (1997).

73 Vesikari T, Esposito S, Prymula R *et al.*; EU Meningococcal B Infant Vaccine Study group. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet* 381(9869), 825–835 (2013).

•• **A comprehensive evaluation showing that 4CMenB is immunogenic in infants and children aged 12 months with no clinically relevant interference with routine vaccines, but increases reactogenicity when administered concomitantly with routine vaccines.**

Websites

101 STIKO. Notice from the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute. The combined vaccine against measles, mumps, rubella and varicella vaccine (MMRV). www.igienistionline.it/docs/2011/24stiko.pdf (Accessed 14 February 2013)

102 National Health System. Central Alerting System. Seasonal flu immunisation programme 2011/12 – Viroflu® vaccine and risk of fever in children under 5 years. www.cas.dh.gov.uk/ViewandAcknowledgement/ViewAlert.aspx?AlertID=101663 (Accessed 14 February 2013)